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STUDY OF PATTERN AND SEVERITY OF ADVERSE EFFECT OF SECOND LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN PEOPLE LIVING WITH HIV AND THEIR CORRELARION TO CD4 COUNT

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ABSTRACT

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Because of treatment failure with first line ART, second line ART is being instituted with free of cost under NACO. **Aims & Objectives:** The aim of this study is to gain knowledge on the severity and pattern of adverse effect of second line HAART drug in patients living with hiv and their correlation with cd4 count in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment. **Material & Methods:** Institution based prospective observational study conducted using review of clinical records and follow up of adult patients started on second line ART from june 2017 to December 2018 at Govt medical college ,miraj . All adult AIDS patients of either sex aged greater than or equal to 20 years who were registered for second line anti-retroviral treatment at Govt medical college ,miraj were included in the study. The clinical records of study subjects were reviewed ADRs. Information on patient's details, duration of treatment, drug details, nature of the adverse drug reactions, severity, outcome, and results of investigations performed were collected using a data collection format (Annex I). Data were collected from june 2017 to December 2018. **Results:** 116 cases were included in the study. Among the total 116 patients who were on second line ARV drugs, ADRs were reported in 89 (76.72%) patients. The most frequently observed ADRs were nausea (30.30%), followed by vomiting (27.27%), diarrhea (21.21%) , loss of appetite (18.18%) and vomiting . Out of the 89 patients who developed ADRs, 39 (45.45 %) patients were grade II, whereas grade 3 and 1. ADRs occurred in 29 (25%) and 21(18.10%) of the patients respectively. Grade IV was reported in none of the patients. No ADRs were noted in 27(23.27%) patients. Mean CD4 count for gastro intestinal, CNS, skin hematological , metabolic ,renal , hepatic are 89.91, 98.17, 72.83, 101.8, 80.63 ,90.5 , 153 respectively **Conclusion:** Second line anti-retroviral drugs are expensive, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS. Though second line ART regimens are associated with mild to moderate ADRs, these are most effective regimens as they improved CD4 counts and reduced viral load significantly.

KEYWORD: Pattern, severity, CD4, HAART, HIV, NACO.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors.[1]

Disease burden

1) HIV is a rapidly evolving pandemic[2] entering its third decade, with cases reported from virtually every country. At present, 33.2 million individuals were living with HIV infection (range: 30.6–36.1 million) according to the Joint United Nations Programmed on HIV/AIDS (UNAIDS).

2) India has the third largest number of HIV positive persons with an estimated 3.8 million infected persons. HIV prevalence is highest in Southeast Asia, with wide variation in trends between different countries.[3]

3) AIDS was first recognized by the U.S. Centers for Disease Control and Prevention in 1981 and its cause HIV, identified in the early 1980s. Although treatments for AIDS and HIV can slow the course of the disease, there is no known cure or vaccine. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, but these drugs are expensive and routine access to antiretroviral medication is not available in all countries.[4]

To respond to the challenge, the Government of India established the National AIDS Committee in 1986, which set the foundation for the establishment of National AIDS Control Organization (NACO) in 1992 to oversee the policies for prevention and control of the infection. The first phase of the National AIDS Control Programme (NACP) started in 1992 and lasted until 1999. This was followed by NACP-II (2000-2005), NACP-III (2006-2011) and NACP-IV (2012-2017). The NACO-1, First phase contained initial interventions focused on understanding modes of transmission and on prevention, blood safety and IEC strategy to increase awareness.[5]

During NACP-II, the programme was decentralized to the states by the establishment of SACS, and focus was laid on blood safety, targeted intervention and low-cost care including management of OIs.

The Antiretroviral Therapy (ART) was introduced in 2004 in the later phase of NACP II. However, the coverage of services was limited to tertiary care centers. NACP-III aimed at reversing the epidemic over the next five years and focused on targeted interventions, district-level interventions, a massive scale-up of services, and quality assurance mechanisms. Reduction in new infections by 50% was a major achievement of NACP-III.

In the current phase of NACP-IV, the focus is on consolidating the gains achieved so far, dealing with emerging vulnerabilities, and balancing between prevention and growing treatment needs. NACP-IV aims at improving integration and mainstreaming HIV care in the general health system.[5]

People Living with HIV/AIDS (PLHA): The total number of people living with HIV/AIDS (PLHA) in India is estimated at 23.9 lakh (19.3 – 30.4 lakh) in 2009. Children under 15 yrs. account for 3.5 percent of all infections, while 83 percent are the in-age group 15-49 years. Of all HIV infections, 39 percent (9.3 lakhs) are among women.[6] The four high prevalence states of South India (Andhra Pradesh–5 lakhs, Maharashtra–4.2 lakhs, Karnataka–2.5 lakhs, and Tamilnadu–1.5 lakhs) account for 55 percent of all HIV infections in the country. The Government of India on November 30, 2003 announced a plan to place 1 lakh AIDS cases in India on anti-retroviral therapy (ART) by the end of 2007 and 15-20% additional AIDS cases each year, thereafter, for a period of 5 years. Till December 2008, 197 ART centers have been established and 1, 99,237 persons have been put on ART in India. The primary goals of ART are maximal and durable reduction in plasma viral load levels, restoration of immunological functions aimed at prolongation of life and improved in quality of life.

Presently there are 15, US FDA approved antiretroviral agents available in India. A combination of at least 3 agents from different classes of anti-retroviral drugs is the regimen of choice (first line ART). Because of treatment failure with first line ART, second line ART is being instituted in many centers in our country.

Govt medical college miraj, being one of them. Antiretroviral therapy (ART) has markedly changed the pattern of infection by the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). Current ART regimens are capable of reducing viral load to undetectable levels with a consequent increase in lymphocyte T-CD4+ counts and a substantial reduction in HIV-associated morbidity and mortality.[1] In spite of ART benefits, adverse reactions to these drugs have been pointed to as one of the main reasons for discontinuation and non-adherence to ART Success of the anti-retroviral treatment is highly dependent on willingness of HIV positive Individuals to adhere to complex ARV regimens.[7] Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of toxic effects, noncompliance or treatment failure within the first 8 months of therapy.[8]

Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients.[9,10] Therefore, many countries have adverse drug reactions (ADR) monitoring centers, which are responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluation is made and safety measures are taken to protect the public from unnecessary harm.

The aim of this study is to gain knowledge on the profile of ADR associated with second line ARV drugs, the burden of adverse drug reactions of second line ART in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

MATERIAL AND METHODS

Study Subjects

Adult patients on second line ART who fulfilled the inclusion criteria of study subject

Study Design

Institution based prospective observational study conducted using review of clinical records and follow up of adult patients started on second line ART from June 2017 to December 2018 at Govt medical college miraj

Sample Size

The total sample size was 116.

Inclusion and exclusion criteria Inclusion criteria

- All adult AIDS patients of either sex aged greater than or equal to 20 years who were registered for second line anti-retroviral treatment at Govt medical college miraj Hospital.

Exclusion criteria

- Patients above 60 and below 20 years of age
- Patients with known hypersensitivity reactions.
- Patients with liver failure and renal failure
- Patients with neuropsychiatric disorders
- Any patient with deliberate or unintended overdose,

missing clinical record, incomplete data or those transferred in after they have been on second line ART for more than one month were excluded from the study.

Study variables

Independent

Socio-demographic variables

Clinical and laboratory state at the beginning of second line ART Second line ART Regimen

Dependent

Pattern of ADRs

Severity of ADRs

Data Collection Procedure

The clinical records of study subjects were reviewed for ADRs. Information on patient's details at the start of ART, duration of treatment, drug details, nature of the adverse drug reactions, severity, outcome, and results of investigations performed were collected using a data collection format (Annex I). Data were collected from June 2017 to December 2018.

Operational definitions

An adverse drug reaction (ADR) is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in human'. A side effect is 'any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which, is related to the pharmacological properties of the drug'. ADRS to ART and Severity grading (See Annex II)

Data Processing and Management

Data entry and analysis were done using Microsoft excel sheet and graph pad prism statistical software. Tables and graphs were used to present frequencies of adverse drug reactions (ADRs) in patients on second line ART. Associations between the independent and dependent variables were tested using OR and 95 % CI was used to measure the strength of the association between the independent and dependent variables.

Ethical Considerations

Study was started after taking approval from the institutional ethics committee of the Govt medical college mirajhospital. Informed consent of the patient was also taken. Confidentiality of the information was assured in such a way that no disclosure of any name of the patient, the health care provider or drug product in relation to the finding was made.

Description of the procedure

Fifty eight patients who are on second line ART drugs due to treatment failure of first line ART drugs have been included in the study based on inclusion and exclusion criteria. The study subjects were monitored for the adverse drug reactions for a period of 18 months. Causality assessment was done by WHO –UPPSALA MONOTORING score and drug adherence rate calculated by pill count method.

Following parameters were monitored Adverse effects

complaints of adverse effects like nausea, vomiting ,diarrhea, abdominal discomfort, flatulence, headache, dry mouth, taste perversion, hyper pigmentation of nails, asthenia, myalgia, myopathy, insomnia, depression, fatigue, malaise, circumoral or peripheral numbness and others if any were recorded.

Vitals-pulse rate, blood pressure, respiratory rate, body weight

Systemic examination

Investigations

Complete blood picture, complete urinary examination, Lipid profile, Liver function tests, Blood urea, Serum creatinine, Serum electrolytes, Random blood sugar.

CD4 count: CD4 count analysis was done by flow cytometric analysis[42] method using CD4 easy count kit.

RESULTS

Socio-demographic distribution of the study population

116 cases were included in the study. The age of patients were ranging from 20–60 years. The Socio-demographic distribution of the population is as shown in table.

Table:1. socio-demographic distribution of the study population on second line ART at Govt medical college, miraj Hospital.

Age in years	No of patients	Percentage of Patients (%)
20-29	10	8.62
30-39	48	47.41
40-49	39	31.90
50-60	14	12.07
Total	**116**	**100**

At the initiation of treatment, 59 Patients (50.86%) weighed below 50 kg and 57(49.14%) weighed more than 50 kg.AT the initiation art 75(64.66%) were male and 41(35.34 %) were females. among them 89 (76.72%) patients had ADR, 27 (23.28%) had no ADR.

TABLE -2

VARIABLES	NUMBER(%)
WEIGHT	
<50kg	59(50.86%)
>50 kg	57(49.14%)
SEX	
Male	75(64.66%)
Female	41(35.34%)
ADR	
Preent	89(76.72%)
Absent	27(23.28%)

Five different regimens of second line ART used for treatment in our study according to NACO guidelines
Out of 116 patients 54 (46.55%) were on TDF+3TC+AT/r, 33(28.45%) patients were on ABC+3TC+AT/r, 27 (23.28%) patients were on ZDV+3TC+AT/r and small percentage (1.72%) of patients were on lopinavir ritonavir-based protease inhibitors regimen

Regimen

Regimen	No of patients	Percentage of Patients
ABC+3TC+AT/R	33	28.45%
ABC+3TC +LP/R	1	0.86%
TDF+3TC+AT/R	54	46.55%
ZDV+3TC+AT/R	27	23.28%
ZDV+3TC+LP/R	1	0.86%
Total	**116**	**100%**

Frequency of ADRs and severity

116 cases were included in the study. Among the total 116 patients who were on second line ARV drugs, ADRs were reported in 89 (76.72%) patients. The most frequently observed ADRs were nausea (30.30%), followed by vomiting (27.27%), diarrhea (21.21%), loss of appetite (18.18%) and vomiting. Out of the 89 patients who developed ADRs, 39 (45.45 %) patients were grade 2, whereas grade 3 and 1. ADRs occurred in 29 (25%) and 21(18.10%) of the patients respectively. Grade IV was reported in none of the patients. No ADRs were noted in 27(23.27%) patients. Mean CD4 count for gastro intestinal, CNS, skin hematological , metabolic ,renal , hepatic are 89.91, 98.17, 72.83, 101.8, 80.63 ,90.5 , 153 respectively.

Most common ADRs were gastrointestinal (38.79%), followed by haematological (11.21%), nuerological (10.34%),dermatological(10.34%),metabolic(6.90%).

Renal toxicity in 9 (7.56%) patients and liver toxicity in 12 (10.34%) patients. Myalgia was observed in 10(8.62%) patients. Among the gastro intestinal, nausea (38.4%) was most common followed by loss of appetite (31.0%), diarrhea (20.10%) and gastritis (16.3%). Among the neurological ADRs, most common ADR was paresthesia (16.3%) followed by insomnia (10.02%) and headache (6.12%). Depression was observed in (2.18%) patients. Among the cutaneous ADRs hair loss (10.34%) was most common followed by xeroderma (6.89%) and rash (6.03%). Hyperpigmentation of nails observed in (5.17%) patients.

Table -3 Distribution and pattern of ADRs to second line ARV drugs at govt medical.

Variables	Number(%)
ADR	
YES	89(76.72%)
NO	27(23.28%)
Types of ADR **Gastro intestinal**	
Nausea	45(38.40%)
Loss of Appetite	36(31.03%)
Vomiting	28(21.14%)
Diarrhea	24(20.19%)
Gastritis	19(16.38%)
Dry Mouth	16(13.79%)
Neurological	
Insomnia	12(10.03%)
Paresthesia	19(16.37%)
Headache	7(6.12%)
Depression	3(2.18%)
Dermatological	
Hair Loss	12(10.34%)
Xeroderma	8(6.89%)
Rash	7(6.03%)
Hyperpigmentation of nails	6(5.17%)
Others	
Anemia	13(11.20%)
Metabolic	6.90%
Hepatic	10.34%
Renal	7.56%
Myalgia	8.62%

Incidence of ADRs in the different variables.

Variables	ADR Present	ADR Absent	OR	95% CI	P Value
Sex					
Male	56(74.66%)	19(25.34%)	2.023	0.84-4.86	0.11
Female	34(82.92%)	07(17.08%)			
Age					
< 40 yrs	47(72.30%)	18(27.70%)	0.84	0.35-2.01	0.69
> 40 yrs	42(82.35%)	9(17.65%)			

Weight					
< 50 Kg	43(66.1%)	16(33.9%)	0.64	0.26-1.53	0.31
> 50 Kg	46(80.7%)	11(19.3%)			
Regimen					
ABC+3TC+AT/R (n=33)	24(72.72%)	9 (27.28%)			
ABC+3TC +LP/R (n=1)	1 (100%)	0 (0%)			
TDF+3TC+AT/R (n=54)	44 (81.48%)	10(18.52%)			
ZDV+3TC+AT/R (n=27)	20 (74.07%)	7 (25.93%)			
ZDV+3TC+LP/R (1)	0 (0%)	1(100%)			

DISCUSSION

The selection of the existing second-line drug regimens were based on the availability of fixed-dose combinations, affordability, toxicity profile, need for laboratory monitoring, coexistent conditions (TB and hepatitis B), potential for maintenance of future treatmentoptions and special considerations for women of childbearing potential. These standardized simplified second line regimens have been essential in expanding access to ART in resource limited countries. If these drugs are not used appropriately, the current second-line regimen will lose its efficacy sooner than it had to. To maximize durability of second line regimen one has to deal with factors that affect the adherence of patients to ART. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.

In this study the second line regimen Out of 116 patients 54 (46.55%) were on TDF+3TC+AT/r, 33(28.45%) patients were on ABC+3TC+AT/r, 27 (23.28%) patients were on ZDV+3TC+AT/r and small percentage (1.72%) of patients were on lopinavirritonavir-based protease inhibitors regimen. Regarding follow up of patients, 116 cases were still on followed UP

In this study, the frequency of ADRs among patients who were on second line ARV drugs was found out to be about in 89 (76.72%). Out of the 89 patients who developed ADRs, majority 39 (45.45 %) patients were grade II, whereas grade 3 and 1. ADRs occurred in 29 (25%) and 21(18.10%) of the patients respectively. Grade IV was reported in none of the patients. None of the ADRs were noted in 27 (23.27%) patients.

There was no significant association between the initial hemoglobin level of the patient at the initiation of treatment and severity of anemia. This may be due to the fact that those with low initial hemoglobin were started on regimen that doesn't have ZDV.

Duration of treatment at the time of diagnosis of ADRs was also significantly associated with the type of ADRs. Anaemia and malaise were reported throughout treatment duration. Nausea, vomiting, diarrhea, gastritis were reported at the initiation of treatment, whereas most Paresthesias, renal toxicity, raised ALT, dyslipidemias were diagnosed beyond 6 months duration. Pancreatitis which was observed in 2 cases was seen after 12 months duration of treatment.

In 116 cases, Association of ADRs in males 75(64.66%) was stronger than females 41(35.34%). 41-60 years age group (59(50.86%) had more ADRs than 20-40 years age group 59(50.86%). Initial weight more than 50 kg group, had more ADRs (79.32%) than less than 50 kg weight group (72.42%). Initial CD4 count less than 100 group, had more ADRs (79.07%) than CD4 count more than 100 groups (66.67%).

Average drug adherence rate was 96% in this study. Causality assessment done by NARANJO score revealed the probable association of ADRs with second line ART.

CONCLUSION

Second line anti-retroviral drugs are expensive, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS. Research to improve current treatments includes decreasing side effects of current drugs, further simplifying drug regimens to improve adherence, and determining the best sequence of regimens to manage drug resistance.

The most frequently diagnosed ADRs were nausea followed by insomnia, loss of appetite, malaise and vomiting. Out of the 44 patients who developed ADRs, majority of patients had grade II, followed by grade III and I ADRs. Grade IV was reported in none of the patients.

Most common ADRs were gastrointestinal followed by neurological, cutaneous and metabolic. None of the socio-demographic variables, the initial clinical and laboratory state were significantly associated with the development of ADRs which needs to be confirmed with further prospective study.

The type of ADRs that the patient developed was very much associated with the duration of treatment. Similarly, the severity of ADRs was also associated with type of ADRs and the duration of treatment.

Though second line ART regimens are associated with mild to moderate ADRs, these are most effective regimens as they improved CD4 counts and reduced viral load significantly.

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